## Remarks/Argument

Claims 14 and 33-51 are pending in the application. By operation of this Amendment, claims 14, 33-42, and 48-50 have been cancelled, claims 43 and 51 have been amended and new claims 52-56 have been added. Claim 43 as amended now specifies that the inactivated human immunodeficiency virus is chemically inactivated by 2,2'-dithiopyridine, the composition expands the *in vivo* expression of virus-specific CD8+ T cells, and the virus-specific CD8+ cells kill HIV-infected cells. Inventors Louis (Wei) Lu and Jean-Marie Andrieu have published an article showing that expansion of the *in vivo* expression of virus-specific CD8+ T cells which kill HIV-infected cells is achieved with pharmaceutical compositions as recited in the pending claims; see Wei et al., *Nature Med.*, vol.10(12), p:1359-65, 2004 (attached).

Support for amended claim 43 is found, for example, in paragraphs [0011] to [0013], [0050], [0065], [0066] and [0086]. Support for new claim 52 is found, for example in paragraph [0071]. Support for new claim 53 is found, for example in paragraph [0047]. Support for new claim 54 is found, for example in paragraphs [0066] and [0071]. Support for new claim 55 is found, for example in paragraph [0065] and [0071]. Support for new claim 56 is found, for example in paragraph [0066] and [0068]. No new matter has been added. In view of the above changes and the following remarks, the Applicants respectfully request reconsideration of the claims.

## Response to the section 102(e) rejection

Claims 14, 33-35, 43 and 45-47 have been rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. 2003/0095988 of Lisziewicz et al. ("Lisziewicz"). According to pg. 3 of the Office Action, "Lisziewicz et al. qualifies as a pharmaceutical composition because it does not include toxic and harmful ingredients," and "thus, a reference teaching a composition that is free of toxic or harmful materials, then the composition of the reference qualifies as a pharmaceutical composition, regardless if the reference suggests a pharmaceutical use of the composition."

The Applicants respectfully disagree. In fact, the composition described in Lisziewicz may indeed contain toxic or harmful ingredients. See, for example, Lisziewicz paragraph

[0146], which describes the isolation and resuspension of PBMCs in "RPMI 1640" cell culture medium. The final resuspension described in this paragraph uses complete RPMI 1640, which contains 10% fetal calf serum ("FCS"). FCS is considered as potentially harmful by FDA and is prohibited in pharmaceutical compositions. For RPMI 1640 without the FCS, the medium still contains phenol red, glutathione, and HEPES (N-2-Hydroxyehtylpiperazine-N'-2-ethanesulfonic acid), which are also considered harmful. Even assuming arguendo that these substances would be considered "non-toxic and not harmful," the mere disclosure of solutions for isolating and resuspending PBMCs is not the same as disclosing a pharmaceutically acceptable carrier. Thus, Lisziewicz et al. cannot anticipate a pharmaceutical composition claim.

Nevertheless, in order to advance prosecution of the present application, the Applicants have amended claim 43 to recite a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an inactivated human immunodeficiency virus, which is chemically inactivated by 2,2'-dithiopyridine (also called aldrithiol-2 or AT-2). This amendment is made without prejudice or disclaimer, and the Applicants reserve the right to pursue any canceled subject matter in a continuing application.

As recognized by the Examiner, Lisziewicz et al. does not teach nor disclose an inactivated human immunodeficiency virus, which is chemically inactivated by 2,2'-dithiopyridine (aldrithiol-2). In light of the foregoing, the Applicants respectfully request withdrawal of the 35 U.S.C. 102(e) rejection of claim 43 and its dependent claims 45-47. As new claims 52-56 depend directly or indirectly on claim 43, these claims are also not anticipated by Lisziewicz.

**Response to the section 103(a) rejections**

Claims 36-38, 41 and 48-50 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lisziewicz in view of Grovit-Ferbas et al. Claims 36-38, 41 and 48-50 have been canceled without prejudice or disclaimer thereof, and thus the rejection is moot.

Claims 39-40, 44 and 51 have been rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lisziewicz in view of Grovit-Ferbas et al., and in further view of Cohen et al. Claims 39-40 have been canceled without prejudice or disclaimer, and the rejection is moot as to these claims. The rejection will be discussed with respect to claims 44 and 51.

Page 5 of the Office Action states that "one of ordinary skill in the art would have a reasonable expectation of success for doing so because Lisziewicz, Cohen et al., and Grovit-Ferbas et al. are analogous to one another, each teaching the use of an antigen pulsed (sic) with dendritic cells." The Applicants respectfully disagree with this contention. None of these references teach or suggest the claimed pharmaceutical composition of the invention, which comprises an effective amount of antigen presenting cells pulsed with 2,2'-dithiopyridine inactivated HIV for expanding *in vivo* expression of virus-specific CD8+ T cells and inducing the killing of HIV-infected cells by said virus-specific CD8+ cells, and a pharmaceutically acceptable carrier. Lisziewicz and Grovit-Ferbas et al. teach the use of a heat inactivated and heat or formaldehyde inactivated antigen pulsed dendritic cells, respectively. Cohen et al. teaches a method for inducing dendritic cells from monocytes which have been isolated from a patient. The dendritic cells are pulsed with autologous tumor antigen, non-autologous, non-HIV derived antigen derived peptide, or HIV surface antigens. Thus, the antigens used in each of these references are different, and one skilled in the art would not expect that each type of antigen would necessarily produce the same response.

The Office Action stated, in the context of the obviousness rejection over Lisziewicz and Grovit-Ferbas discussed above, that "it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to substitute one known method of viral inactivation for another with a reasonable expectation of success," and that "the (CD8+ T) cells would necessarily kill HIV infected cells" because this property was allegedly an inherent property of virus-specific CD8+ T cells.

The ability of the claimed pharmaceutical composition to expand *in vivo* expression of virus-specific CD8+ T cells which then kill HIV-infected cells are positively recited features of claims 44 and 51. The claimed features result from the pulsing of antigen-presenting cells by HIV virus inactivated by 2,2'-dithiopyridine. There is no teaching or suggestion in any of the cited references that pulsing dendritic cells with heat inactivated HIV, HIV surface antigens or HIV inactivated by other chemical means would necessarily result in cells that expand *in vivo* expression of virus-specific CD8+ T cells which then kill HIV-infected cells.

For example, Grovit-Ferbas et al. disclose a dendritic cell which contains heat-inactivated recombinant HIVsx. This dendritic cell was able to induce a cell-mediated recall response *in vitro*, as measured by the capacity to induce gamma interferon production in the PBMCs isolated

from three HIV patients, none of whom had a detectable viral load. No data is presented in Grovit-Ferbas et al. which shows that the dendritic cells of Grovit-Ferbas et al. expanded CD8+T cells, or was capable of inducing the CD8+T cells to kill HIV-infected cells. In fact, according to Grovit-Ferbas et al., pg. 5808, 2nd column (emphasis added):

> Although it is not clear which cell subset produced IFN-γ in response to our vaccine preparation, it is likely that the cytokine was secreted by ***CD4*** cells, since the DC were given an exogenous (antigen) for processing.

Grovit-Ferbas et al. also teach the inactivation of HIV-1 with formaldehyde alone, or with heat and formaldehyde. When the HIV-1 is treated only with formaldehye, or treated first with formaldehyde and then with heat, binding of gp120 surface protein to neutralization epitopes was significantly reduced. In contrast, treatment of HIV-1 with heat alone, or first with heat and then with formaldehyde, did not reduce (and sometimes enhanced) epitope binding. Thus, formaldehyde treatment is clearly altering the conformation of HIV-1 surface antigens. Treatment of HIV with 2,2'-dithiopyridine does not cause any such conformational changes (see paragraph [0010] bridging pgs. 17-18 of the Applicants' specification). One skilled in the art would therefore not consider formaldehyde treatment of HIV analogous to treatment with 2,2'-dithiopyridine.

Grovit-Ferbas also discusses the injection of SIV inactivated with 2,2'-dithiopyridine into a juvenile pig-tailed macaque, which induced expression of anti-SIV antibodies. However, one skilled in the art would understand that the induction of antibodies is a humoral immune response, which is not necessarily indicative of (or even connected to) a T-cell mediated immune response. Moreover, Grovit-Ferbas admits that efforts to model a killed HIV-1 vaccine with SIV in macaques has proven to be problematic.

The inventors have also shown that CD8+T cells expanded by thermally inactivated HIV virus-pulsed dendritic cells do not kill HIV infected cells, whereas CD8+T cells specifically expanded by aldithriol-2 (2,2'-dithiopyridine) inactivated HIV virus-pulsed dendritic cells kill HIV infected cells. *See* the attached Declaration of Louis (Wei) Lu. These results show that the (i) expansion of expression of CD8+ T cells, and the (ii) killing of HIV-infected cells by expanded virus-specific CD8+ cells corresponds to two distinct properties, which are not necessarily correlated, and which results specifically from antigen-presenting cells pulsed with

aldrithiol-2 inactivated HIV virus. Thus, one skilled in the art would not consider formaldehyde treatment of HIV analogous to treatment with 2,2'-dithiopyridine.

Cohen et al. does not describe dendritic cells pulsed with an inactivated non-recombinant HIV virus, but only with isolated HIV surface antigens. One skilled in the art would understand that such isolated HIV surface antigens would not retain the native conformation and fusogenic activity of surface antigens located on intact HIV particles. Further, Cohen et al. fails to discuss any *in vivo* treatment efficacy from the administration of dendritic cells challenged with antigens from the surface of HIV-1, let alone from dendritic cells pulsed with an inactivated non-recombinant HIV virus. None of the data presented in Cohen et al. is predictive of how dendritic cells would specifically interact with non-recombinant inactivated HIV virus, or of how dendritic cells pulsed with the virus would be able to elicit a protective immune response after administration to a patient. Thus, Cohen et al. utterly fails to make any showing of efficacy in treating an HIV patient using even the dendritic cells challenged with antigens mentioned therein, and certainly not using dendritic cells pulsed with an inactivated non-recombinant HIV virus as recited in claims 44 and 51.

One skilled in the art would therefore have no motivation to combine the teachings of Lisziewicz, Grovit-Ferbas et al. and Cohen et al. to produce the pharmaceutical compositions of claims 44 and 51, as each of these references teaches the use of HIV antigens with properties that differ widely from each other and from HIV inactivated with 2,2'-dithiopyridine. A fair reading of the cited references, either alone or in combination, would also provide one skilled in the art with no reasonable expectation that a pharmaceutical composition as recited in claims 44 and 51 (which depend from claim 43) could be successfully made. In light of the foregoing, the Applicants respectfully request withdrawal of the 35 U.S.C. 103, (a) rejection of claims 44 and 51.

New claims 52-56 also depend either directly or indirectly from claim 43, and thus are also not rendered obvious by Lisziewicz, Grovit-Ferbas et al. and/or Cohen et al.

The Applicants respectfully submit that the claims are now in condition for allowance, which is respectfully requested. If the Examiner believes that further minor amendments or corrections as to matters of form will advance the case, the Examiner is invited to telephone the Applicants' undersigned representative.

Respectfully submitted,

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